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PERSPECTIVE/OPINION

No Evidence for Differential Relations of Hedonic Well-Being and Eudaimonic Well-Being to Gene Expression: A Comment on Statistical Problems in Fredrickson et al. (2013)

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In a study of the relation between well-being and gene expression, Fredrickson et al. (2013, *Proceedings of the National Academy of Sciences of the USA, 110* (33), 13684–13689) concluded that hedonic well-being and eudaimonic well-being have similar affective correlates but different gene transcriptional correlates in human immune cells. This comment addresses four statistical problems in Fredrickson et al.'s (2013) analyses. First, an idiosyncratic two-factor scoring rather than the documented and well-validated three-factor scoring was used for the instrument assessing well-being. Second, the analyses relating hedonic well-being and eudaimonic well-being to affect did not include the same variables as the analyses relating these two well-being variables to gene expression, invalidating any comparison between them. Third, hedonic well-being and eudaimonic well-being were highly correlated, resulting in untheorized and unrecognized suppression effects that accounted for their supposed differential relations with gene expression. Fourth, the method of computing p values for the one-sample t tests discarded information and violated the assumption of independence for those tests. These problems cast considerable doubt on the validity of Fredrickson et al.'s (2013) conclusions.

Keywords: factor analysis; gene regulation; regression analysis; social genomics; statistical models; suppression; well-being

In a recent study of the relation between well-being and gene expression, Fredrickson et al. (2013) concluded that hedonic well-being and eudaimonic well-being have "similar affective correlates" (p. 13684) but "markedly divergent gene transcriptional correlates in human immune cells" (p. 13686). Specifically, they asserted that hedonic well-being and eudaimonic well-being showed "comparably strong positive relationships to total well-being and comparably strong inverse relationships to depressive symptoms, and were highly correlated with one another" (p. 13686). In contrast, hedonic well-being was positively related to gene expression for the overall set of genes under consideration and for the subset of pro-inflammatory genes, (marginally) negatively related to gene expression for the subset of genes involved in antibody synthesis, and not related to gene expression for the subset of genes mediating Type I interferon antiviral responses, whereas eudaimonic well-being was generally related to the opposite pattern of gene expression.

A number of statistical problems in Fredrickson et al.'s (2013) study cast considerable doubt on the validity of these conclusions. First, an idiosyncratic two-factor scoring rather than the documented and well-validated three-factor scoring was used for the items in the instrument assessing well-being. Second, the analyses relating hedonic well-being and eudaimonic well-being to affect did not include the same variables as the analyses relating these two well-being variables to gene expression, invalidating any comparison between them. Third, hedonic well-being and eudaimonic well-being were highly correlated, resulting in untheorized and unrecognized suppression effects that accounted for the supposed differential relations of these two well-being variables to gene expression. Fourth, the method of computing p values for the one-sample t tests discarded information and violated the assumption of independence for those tests. In this comment, I present the results of my reanalysis of Fredrickson et al.'s (2013) dataset as the basis for a detailed discussion of these statistical problems. I first describe the changes necessary to Fredrickson et al.'s (2013) publicly available dataset (https://www.ncbi.nlm.gov/geo/; accession number GSE45330; March 20, 2013) before it could be reanalyzed.

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Changes to the Dataset

Fredrickson et al. (2013) indicated that their sample consisted of 84 healthy adults who completed a 14-item instrument assessing well-being and provided demographic and health-related information. Of these 84 cases (participants), 80 provided blood samples for transcriptome analysis, and when Fredrickson et al. (2013) reported a sample size for an analysis (e.g., Figure 1, p. 13686), it equaled 80. The dataset contains only 79 cases, however. Two of these 79 cases are missing all demographic and health-related information, and a third is missing information about alcohol consumption. Fredrickson et al. (2013, Supporting Information, p. 1) indicated that they used SAS 9.3 for their analyses. In a regression analysis, SAS ordinarily deletes any case for which any variable in the analysis has a missing value, unless a value for that variable is imputed. Fredrickson et al. (2013) did not indicate that they imputed values for variables with missing values, so I have omitted these three cases from all of my analyses. Six of the remaining 76 cases are missing responses to one (five cases) or two (one case) of the items in the instrument used to assess well-being. Fredrickson et al. (2013) seem to have computed scores (means) for hedonic well-being and eudaimonic well-being ignoring items with missing values, and I have done the same. Another case has an invalid value ("4") for race/ethnicity, apparently a mistake made in converting the four race/ethnicity categories shown in Fredrickson et al.'s (2013) **Table 1** (p. 13685) to the dichotomous variable nonwhite/white; for this case, I have changed race/ethnicity to nonwhite ("0"). These changes resulted in a dataset with 76, not 79 or 80, usable cases. Fredrickson et al. (2013) standardized the scores for hedonic well-being and eudaimonic well-being for use in their analyses; I have re-standardized these scores across the 76 usable cases. All of my analyses are based on these 76 cases and performed in SAS 9.3.

The results of my independent review of Fredrickson et al.'s (2013) dataset agreed with the results of a similar review reported by Brown, MacDonald, Samanta, Friedman, and Coyne (2014, Supporting Information, pp. 2–4). I note that, in an updated (July 15, 2014) version of the dataset, the invalid race/ethnicity value of "4" appearing in the original version has been changed to "0," although I can find no explicit mention of this change. Additionally, a more recent article by Fredrickson et al. (2015, **Figure 1**, p. 5) reported the sample size in the Fredrickson et al. (2013) study to have been 76, indicating that the sample size of 80 reported by Fredrickson et al. (2013) must not have been correct.

The Factor Structure and Scoring for the Well-Being Instrument

Fredrickson et al. (2013) assessed hedonic well-being and eudaimonic well-being with an instrument that they called the "Short Flourishing Scale" (article, pp. 13684, 13688, Supporting Information, p. 1) that actually is named the "Mental Health Continuum Short Form" (MHC–SF, Keyes, 2009a). (Fredrickson et al., 2013, may have confused the MHC–SF with the "Flourishing Scale" developed by Diener et al., 2010, that is sometimes called the "Short Flourishing Scale" [e.g., http://ogg.osu.edu/media/documents/MB%20Stream/ShortFlourishingScale.pdf].) The MHC–SF consists of 14 items assessing emotional well-being (three items), social well-being (five items), and psychological well-being (six items) on a six-point scale and is an abbreviated version of the original longer instrument ("Mental Health Continuum–Long Form," Keyes, 2008, available from http://booksite.elsevier.com/9780123745170). The non-orthogonal three-factor structure underlying both the long form and the short form of this instrument has been validated repeatedly (e.g., Gallagher, Lopez, & Preacher, 2009; Jaotombo, 2014; Joshanloo, Rostami, & Nosratabadi, 2006; Joshanloo, Wissing, Khumalo, & Lamers, 2013; Karaś, Cieciuch, & Keyes, 2014; Keyes, 2005, 2009b; Keyes et al., 2008; Lamers, Westerhof, Bohlmeijer, ten Klooster, & Keyes, 2011; Lim, 2014; Petrillo, Capone, Caso, & Keyes, 2015; Robitschek & Keyes, 2009; Salama-Younes, 2011a,b; Salama-Younes & Ismaïl, 2011). Emotional well-being reflects the traditional philosophical concept of hedonia; psychological well-being and social well-being reflect two different aspects of the traditional philosophical concept of eudaimonia.

In his letter to the editor regarding Fredrickson et al.'s (2013) study, Coyne (2013) asserted that the high correlation ($r = .79$) between hedonic well-being and eudaimonic well-being indicated that these two variables were interchangeable and so invalidated the results of Fredrickson et al.'s (2013) analyses, which used both well-being variables as predictors. In their reply to Coyne, Cole and Fredrickson (2013) stated that they addressed this issue "through exploratory and confirmatory factor analyses of the items measuring hedonic and eudaimonic well-being. Consistent with previous observations (e.g., references 6, 14, and 27 from original article), both analyses rejected a single common factor solution in favor of a two-factor solution" (p. E4184).

Cole and Fredrickson's (2013) reply to Coyne (2013) was misleading because it implied that their two factors represented hedonic well-being and eudaimonic well-being. Brown et al. (2014) subsequently performed exploratory and confirmatory factor analyses of the 14 items in the MHC–SF for Fredrickson et al.'s (2013) dataset. They confirmed a two-factor solution but did not find that the three emotional well-being items loaded on one hedonic factor and the remaining five social well-being items and six psychological well-being items loaded on a second eudaimonic factor, as should have been the case. Instead, all three emotional well-being items, two of the social well-being items, and the six psychological well-being items loaded on one factor; the remaining three social well-being items loaded on a second factor. In reply, Cole and Fredrickson (2014) criticized Brown et al. (2014) for attempting to re-factor the MHC–SF "in a sample too small to support reliable factor discovery or item reallocation" (p. E3581). It *is* the case that Fredrickson et al.'s (2013) sample was too small for "reliable factor discovery," but it must be noted that Cole and Fredrickson (2013) re-factored the MHC–SF for that very same small sample

to demonstrate to Coyne (2013) that in their dataset the MHC–SF was best described by two factors, not one.

The results of my independent exploratory and confirmatory factor analyses of Fredrickson et al.'s (2013) dataset using SAS agreed with those of Brown et al. (2014), who used SPSS and AMOS for their factor analyses. Accordingly, I requested a copy of the SAS program that Cole and Fredrickson (2013) used to perform their factor analyses. Examination of that program showed that Cole and Fredrickson (2013) failed to rotate the factor pattern as was needed to interpret the results of the exploratory factor analysis. Had they done so, their results would have been identical to those obtained by Brown et al. (2014) and by me. Demonstrating a two-factor solution for the MHC–SF items for their dataset was necessary but not sufficient for Fredrickson et al. (2013) to have used those two factors as predictors in their regression analyses; they needed to have demonstrated also that the three hedonic items loaded on one factor and the eleven other items on the other factor. They did not so demonstrate.

Cole and Fredrickson (2013) surely must have been aware that it has been shown that the MHC–SF has a three-factor, not a two-factor, structure. Fredrickson et al. (2013) cited the documentation for the MHC–SF (Keyes, 2009a; their article reference 52) which lists several articles providing evidence that both the long form and the short form (and in one instance, an augmented form) of the MHC have a non-orthogonal three-factor structure. Indeed, Fredrickson et al. (2013) themselves cited one of the articles (Lamers et al., 2011; their article reference 38) that validated the three-factor structure. Other articles co-authored by Fredrickson (Catalino & Fredrickson, 2011; Fredrickson & Losada, 2005) also make it clear that she, at least, was familiar with the three-factor structure of the MHC–SF.

Also misleading in the reply to Coyne (2013) were Cole and Fredrickson's (2013) references for a two-factor structure of the MHC–SF. Both the original article and the reply to Coyne ignored all of the articles listed in the documentation for the MHC–SF (Keyes, 2009a) as validating a three-factor structure and instead stated that the two-factor structure that they found was consistent with references 6, 14, and 27 in their original article. Reference 6 (Friedman, 2012) is a literature review of the relations between aging, well-being, and immunity. This review explicitly stated that "most studies of well-being have not examined the empirical independence of these conceptually different traditions" (p. 54). No correlations were reported in this review, nor were the results of any factor analyses; brief mention was made of the fact that a few studies have found that hedonic well-being and eudaimonic well-being are independent or weakly correlated, findings that are not consistent with Fredrickson et al.'s (2013) correlation of .79. Reference 14 (Waterman, 1993) is an empirical study of convergent and divergent validity. The MHC was not used, and no factor analyses were reported. Reference 27 (Keyes, Shmotkin, & Ryff, 2002) is co-authored by Corey L. M. Keyes, the developer of the MHC. This early empirical study included items measuring only emotional well-being (called subjective well-being)

and psychological well-being, not social well-being. Thus, only two of the three kinds of items now included in the MHC were used in this study, and it is not surprising that a two-factor structure rather than a three-factor structure was validated. These three at best marginally relevant references should not have been cited as evidence for a two-factor structure of the MHC–SF when several studies specifically confirming its three-factor structure were listed in the documentation for the MHC–SF and also otherwise known to Fredrickson and her co-authors.

Surprisingly, in their reply to Brown et al. (2014), Cole and Fredrickson (2014) insisted that their division of the 14 MHC–SF items into those assessing hedonic well-being and those assessing eudaimonic well-being was based on the developer's established "scoring," "allocation," or "specification" (article, p. E3581, Supporting Information, pp. 16, 22, 27) of those items, asserting that this scoring was based on multiple previous confirmatory factor analyses in studies totaling thousands of participants (Supporting Information, p. 27). It is certainly the case that there have been many previous factor analyses of the MHC involving thousands of participants. But the claim that these studies supported a two-factor hedonic/eudaimonic scoring is simply wrong. All of these studies have validated a non-orthogonal three-factor structure for the MHC. To the best of my knowledge, the developer of the MHC has nowhere combined nor suggested combining the five social well-being items and the six psychological well-being items into one eudaimonic factor. It *is* the case that he (Keyes, 2009a) labeled the emotional well-being factor as "hedonic" and both the social well-being factor and the psychological well-being factor as "eudaimonic" in the documentation for the MHC–SF He did so not as an indication of the factor structure or scoring of the MHC–SF, but as a way of relating these factors to the traditional philosophical concepts of hedonia and eudaimonia and of describing how these factors were to be used to categorize mental-health status. Brown et al.'s (2014) criticism of Cole and Fredrickson's (2014) factor analyses is a pro-pos because, as I will show later when I raise the question of whether the unrecognized suppression effects in Fredrickson et al.'s (2013) analyses have theoretical importance or are merely statistical artifacts, analyses using the documented and well-validated three-factor scoring of the 14 MHC–SF items do not give the same results as analyses using Fredrickson et al.'s (2013) idiosyncratic two-factor hedonic/eudaimonic scoring.

The Affective Correlates of Well-Being

Fredrickson et al. (2013) reported that symptoms of depression, as assessed by the Center for Epidemiological Studies–Depression (CES–D) instrument (Radloff, 1977), had similarly strong correlations of $-.67$ and $-.66$ ($p = .8550$) with hedonic well-being and eudaimonic well-being, respectively. They also reported that the CES–D subscale assessing affective symptoms of depression had similarly strong correlations of $-.75$ and $-.71$ ($p = .3228$) with hedonic well-being and eudaimonic well-being, respectively, and that the CES–D subscale assessing vegetative symptoms of depres-

Gene	Correlation With Well-Being		*p* for Meng's *Z*
	Hedonic	Eudaimonic	
Type I interferon viral response genes			
IFIT1L	−.25	−.32	.3216
GBP1	−.02	−.03	.8066
IFI16	−.19	−.16	.6263
IFI27	−.08	−.10	.8164
IFI27L1	.00	.03	.7445
IFI27L2	−.04	−.14	.1492
IFI30	−.12	−.17	.3988
IFI35	−.06	−.07	.9313
IFI44	.12	.08	.5921
IFI44L	.09	.06	.6548
IFI6	.07	.02	.5242
IFIH1	−.09	−.05	.5403
IFIT1	.20	.19	.8647
IFIT2	.24	.19	.5099
IFIT3	.19	.20	.9833
IFIT5	−.03	−.05	.7345
IFITM1	.23	.29	.4272
IFITM2	.15	.16	.8820
IFITM3	.00	.03	.7168
IFITM4P	.11	.04	.3684
IFITM5	−.05	.01	.4925
IFNB1	.02	.07	.5192
IRF2	−.10	−.02	.2957
IRF7	.12	.10	.8232
IRF8	−.15	−.17	.8623
MX1	.13	.17	.5763
MX2	.02	.03	.9503
OAS1	−.08	−.06	.7711
OAS2	−.06	−.07	.8951
OAS3	.12	.09	.7038
OASL	.13	.14	.9383
Mean	.04	.02	.7919
Antibody synthesis genes			
IGJ	.03	.14	.1480
IGLL1	−.03	.10	.0925
IGLL3	.02	.02	.9943
Mean	.01	.11	.2033
Pro-inflammatory genes			
IL1B	.17	.09	.2859
IL8	.20	.18	.7364

Gene	Correlation With Well-Being		*p* for Meng's *Z*
	Hedonic	**Eudaimonic**	
FOS	.10	.10	.9912
FOSB	.10	.04	.3891
FOSL1	.06	−.09	.0537
FOSL2	.11	.06	.4922
IL1A	.15	.03	.1272
IL6	.07	.02	.4521
JUN	.06	.06	.9892
JUNB	.02	.02	.9538
JUND	.07	.07	.9159
NFKB1	.04	.11	.3663
NFKB2	.09	.06	.6610
PTGS1	−.13	−.20	.3741
PTGS2	.14	.10	.6116
REL	.06	.03	.6189
RELA	.17	.18	.9399
RELB	.10	.04	.3922
TNF	.18	.09	.2562
Mean	.14	.09	.4935
Omnibus mean	.08	.04	.5912

Table 1: Comparison of the Correlation Between Hedonic Well-Being and Gene Expression to the Correlation Between Eudaimonic Well-Being and Gene Expression for 53 Genes.

Note: Each Pearson's *r* correlation was based on 76 cases. The *p* values for Meng's *Z* were not adjusted for multiple comparisons. For the correlations based on mean gene expression, gene expression was averaged across the genes in each of the three subsets of genes. For the omnibus set of genes, gene expression was averaged across the genes in the entire set of genes, after first having weighted the expression of the Type I interferon viral response genes and the antibody synthesis genes by −1, following Fredrickson et al. (2013).

sion had similarly strong correlations of −.45 and −.48 (*p* = .6297) with hedonic well-being and eudaimonic well-being, respectively. No information about depression is included in Fredrickson et al.'s (2013) publicly available dataset, so it was not possible to verify these correlations.

Fredrickson et al. (2013) also reported that hedonic well-being and eudaimonic well-being showed comparably strong positive relations to total well-being, although they did not provide any details about this analysis or report the actual correlations. Fredrickson et al. (2013) indicated that they had standardized hedonic well-being and eudaimonic well-being prior to their use in the analyses. If two standardized variables are summed, the correlation of one variable with the total equals the correlation of the other variable with the total. This is a statistical fact, not an empirical finding. If hedonic well-being and eudaimonic well-being are standardized before being summed, then the correlation of each with the total equals .94882. If they are not standardized before being summed, then the correlations of hedonic well-being and eudaimonic well-being with the total equal .94926 and .94838, respectively, neither surprising nor interesting

given that the correlation between them equals .80053. (These correlations are computed on the corrected sample of 76 usable cases.)

Although Fredrickson et al. (2013) compared the relations of hedonic well-being and eudaimonic well-being to depression and total well-being to the relations of these two well-being variables to gene expression, these comparisons were not valid because the analyses on which the comparisons were based were not the same. The analyses relating hedonic well-being and eudaimonic well-being to the three depression variables and to total well-being included only one or the other of the two well-being variables, whereas the analyses relating hedonic well-being and eudaimonic well-being to gene expression included both. The analyses relating hedonic well-being and eudaimonic well-being to the three depression variables and to total well-being also did not include any covariates, whereas the analyses relating hedonic well-being and eudaimonic well-being to gene expression did. As will be seen, the inclusion of both of the two well-being variables and of the 15 covariates has important consequences for the results of the analyses.

The Differential Relations of Hedonic Well-Being and Eudaimonic Well-Being to Gene Expression

To examine Fredrickson et al.'s (2013) claim that hedonic well-being and eudaimonic well-being were differentially related to gene expression, I present the results of the following sequence of analyses: (a) two sets of correlational analyses relating well-being to gene expression, the first set analogous to the analyses used by Fredrickson et al. (2013) to relate hedonic well-being and eudaimonic well-being to depression and to total well-being, the second set relating hedonic well-being and eudaimonic well-being to averaged gene expression; (b) three sets of regression analyses relating hedonic well-being and eudaimonic well-being to averaged gene expression; (c) three sets of regression analyses relating hedonic well-being and eudaimonic well-being to averaged gene association; and (d) an examination of suppression effects in the regression analyses. Note that these analyses use Fredrickson et al.'s (2013) two-factor scoring of the MHC–SF, not the documented and well-validated three-factor scoring, because my intention is to rebut Fredrickson et al.'s (2013) and Cole and Fredrickson's (2013) claims that the results of their analyses were not affected by the high correlation between hedonic well-being and eudaiamonic well-being.

Correlational Analyses

To render the analyses relating hedonic well-being and eudaimonic well-being to gene expression comparable to Fredrickson et al.'s (2013) analyses relating hedonic well-being and eudaimonic well-being to depression and to total well-being, I computed the correlation of each of the two well-being variables to gene expression for each of the 53 genes included in Fredrickson et al.'s (2013) study and compared the difference between them using a test for dependent correlations, as had Fredrickson et al. (2013) in testing the difference between the correlation of each of the two well-being variables with depression and with total well-being. Fredrickson et al. (2013) did not state which of several available tests for the difference between dependent correlations they used; I have used Meng's Z (Meng, Rosenthal, & Rubin, 1992). The correlations and p values for Meng's Z from my analysis are shown in **Table 1**. Examination of the p values in this table shows that the correlation between hedonic well-being and gene expression and the correlation between eudaimonic well-being

and gene expression are not significantly different from one another for any of the 53 genes. Most of the differences between the two correlations are quite small, and for only three pairs of correlations is there a sign reversal. Thus, hedonic well-being and eudaimonic well-being do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

But Fredrickson et al. (2013, Supporting Information, p. 1) stated that they did not perform any statistical testing

> at the level of individual transcript-phenotype [single-gene] associations because the goal of this study is not to discover reliable associations between the expression of individual transcripts and measured levels of hedonic or eudaimonic well-being. The goal of this study is to test associations between eudaimonic and hedonic well-being and average levels of expression of specific sets of genes selected a priori for analysis here based on their previously observed involvement in the conserved transcriptional response to adversity (CTRA) (e.g., as representative pro-inflammatory genes, IFN-related genes, and antibody-synthesis related genes) .... [The] primary focus of this study involves testing potential differences in association of hedonic vs. eudaimonic well-being with average expression of one set of 53 genes selected a priori.

Analyzing the relation of well-being to the averaged expression of sets of similar genes, rather than to the expression of single genes, is not unreasonable. For example, if one considers a gene to be analogous to an item in a multi-item test, then one can conceive of averaging gene expressions for subsets of similar genes and for the entire set of genes to be similar to the construction of the subscales and the total scale of the test. Cronbach's alpha equals .91, .82, .91, and .89 for the subset of 31 Type I interferon viral response genes, the subset of 3 antibody synthesis genes, the subset of 19 pro-inflammatory genes, and the "omnibus" set of all 53 genes, respectively; these values of Cronbach's alpha are well above the usual .70 "acceptable" criterion. (Following Fredrickson et al., 2013, Supporting Information, p. 2, in computing Cronbach's alpha, each Type I interferon viral response gene and antibody synthesis gene was weighted by –1 in the omnibus set of genes.)

Gene Set	Number of Genes	Relation to Well-Being	
		Hedonic	Eudaimonic
Omnibus	53	positive	negative
Type I interferon viral response genes	31	negative	positive
Antibody synthesis genes	3	negative	positive
Pro-inflammatory genes	19	positive	negative

Table 2: Relations of Hedonic Well-Being and Eudaimonic Well-Being to Gene Expression Expected by Fredrickson et al. (2013).

Fredrickson et al.'s (2013) expectations for the relation of hedonic well-being and eudaimonic well-being to the averaged expression of the omnibus set of genes and its three subsets are shown in **Table 2**. The omnibus set of genes and the subset of pro-inflammatory genes were expected to be up-regulated by (have a positive relation to) hedonic well-being and down-regulated by (have a negative relation to) eudaimonic well-being. In contrast, the subset of Type I interferon viral response genes and the subset of antibody synthesis genes were expected to be down-regulated by hedonic well-being and up-regulated by eudaimonic well-being. **Table 3** presents Fredrickson et al.'s (2013) results. As expected, the omnibus set of genes and the subset of pro-inflammatory genes had significant positive relations to hedonic well-being. The omnibus set of genes also had a significant negative relation to eudaimonic well-being, but the negative relation between the subset of pro-inflammatory genes and eudaimonic well-being was not significant. Also as expected, the subset of Type I interferon viral response genes had a significant positive relation to eudaimonic well-being; the positive relation between the subset of antibody synthesis genes and eudaimonic well-being was marginally significant. The negative relation between the subset of antibody synthesis genes and hedonic well-being was marginally significant; the relation between the subset of Type I interferon viral response genes and hedonic well-being was positive rather than negative, and not significant. Note that Fredrickson et al.'s (2013) regression analyses included both of the two well-being variables and the 15 covariates as predictors of gene expression.

Accordingly, to analyze the relation between well-being and averaged gene expression, I first averaged gene expressions across the genes in each of the three subsets of specific genes. For the omnibus set of genes, I averaged gene expressions across the genes in the set of all 53 genes, after having first weighted the expression of each Type I interferon viral response gene and antibody synthesis gene by –1. I then computed the correlation of each of the two well-being variables with averaged gene expression for each of these four sets of genes and compared the difference between them using Meng's *Z*. These statistics are also shown in **Table 1** on the lines labeled "Mean." Examination of the *p* values for the four pairs of means in this table shows that the correlation between hedonic well-being and averaged gene expression and the correlation between eudaimonic well-being and averaged gene expression are not significantly different for any of the four sets of genes. For example, for the omnibus set of genes, the correlations between hedonic well-being and eudaimonic well-being and averaged gene expression equal .08 and .04, respectively (*p* = .5912). Even if one of these correlations had a negative sign, it would seem a considerable overstatement to claim that hedonic well-being and eudaimonic well-being have "markedly divergent" relations to gene expression. Again, hedonic well-being and eudaimonic well-being do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

Regression Analyses for Averaged Gene Expression

Because Fredrickson et al. (2013) used regression instead of correlation in their analyses relating hedonic well-being and eudaimonic well-being to gene expression, I next performed eight regression analyses, each predicting averaged gene expression from either hedonic well-being *or* eudaimonic well-being for one of the four sets of genes. **Table 4** shows that both hedonic well-being and eudaimonic well-being have a positive but nonsignificant relation to averaged gene expression for every set of genes. Thus, as in the correlational analysis of single genes, hedonic well-being and eudaimonic well-being do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

But although Fredrickson et al.'s (2013) analyses relating hedonic well-being and eudaimonic well-being to depression and to total well-being included only one or the other of the two well-being variables, their regression analyses relating hedonic well-being and

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Effect	*p*[a]	Effect	*p*[a]
Omnibus	53	positive large	.0047	negative large	.0045
Type I interferon viral response genes	31	positive small	——	positive medium	.0084
Antibody synthesis genes	3	negative large	.0776	positive large	.0849
Pro-inflammatory genes	19	positive large	.0008	negative small	——

Table 3: Relations of Hedonic Well-Being and Eudaimonic Well-Being to Gene Expression Reported by Fredrickson et al. (2013).

Note: Following Fredrickson et al. (2013), the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 for inclusion in the omnibus set of genes. Fredrickson et al. (2013) did not report exact effect sizes; those shown have been estimated from the –2SD to +2SD fold differences in Figure 2 (p. 13686) of their article. The *p* values reported by Fredrickson et al. (2013) apparently were not adjusted for multiple comparisons.

[a] Unreported *p* values are indicated by ——.

eudaimonic well-being to gene expression included both. Fredrickson et al. (2013) apparently (and mistakenly) believed that including both well-being variables in their regression analyses would result in "a purified index of eudaimonic well-being (purged of shared variance with hedonia)" (p. 13687) and "a purified index of hedonic well-being (purged of shared variance with eudaimonia)" (p. 13687). I repeated my regression analyses but predicted averaged gene expression from both hedonic well-being and eudaimonic well-being for each set of genes; the results of the four regression analyses are shown in **Table 5**. Examination of this table shows that the signs of some of the partial regression coefficients have reversed compared to those of the simple regression coefficients in **Table 4**, so that, with the exception of those for the subset of Type I interferon viral response genes, the signs in **Table 5** are consistent with those expected by Fredrickson et al. (2013). However, none of the partial regression coefficients in **Table 5** is significant. Note that, with one exception, the magnitudes of the partial regression coefficients in **Table 5** are larger than those of the simple regression coefficients in **Table 4**, not smaller, as one might expect. Again, hedonic well-being and eudaimonic well-being do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

Finally, I repeated the regression analyses but predicted averaged gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates. Examination of the results presented in **Table 6** shows that the sign of one additional partial regression coefficient (that for eudaimonic well-being in the regression predicting averaged gene expression of the subset of Type I interferon viral response genes) has reversed, so that, with one exception, the pattern of signs is now consistent with the pattern expected by Fredrickson et al. (2013) and completely consistent with the pattern that they reported. However, as in **Tables 4** and **5**, none of the partial regression coefficients in **Table 6** is significant. Again, hedonic well-being

and eudaimonic well-being do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

Regression Analyses for Averaged Gene Association

Although Fredrickson et al. (2013, Supporting Information) initially stated that the goal of their study was "to test associations between eudaimonic and hedonic well-being and average levels of expression of specific genes selected a priori" (p. 1), there was subsequently a subtle and unexplained shift to analyzing "average gene set *association*" (p. 2) [italics mine] instead of average gene set *expression*. Fredrickson et al. (2013) did not in fact average gene expressions across the genes in the omnibus set of genes and each of the three subsets of specific genes and then perform four regression analyses, each predicting averaged gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates for one of the four sets of genes.

Instead, they performed 53 separate regression analyses, in which they regressed gene expression for one gene separately on hedonic well-being, eudaimonic well-being, and the 15 covariates. They then sorted the partial regression coefficients for hedonic well-being and for eudaimonic well-being from these 53 regression analyses into eight sets: (a) hedonic well-being for all 53 genes, (b) hedonic well-being for the 31 Type I interferon viral response genes, (c) hedonic well-being for the 3 antibody synthesis genes, (d) hedonic well-being for the 19 pro-inflammatory genes, (e) eudaimonic well-being for all 53 genes, (f) eudaimonic well-being for the 31 Type I interferon viral response genes, (g) eudaimonic well-being for the 3 antibody synthesis genes, and (h) eudaimonic well-being for the 19 pro-inflammatory genes. The partial regression coefficients for hedonic well-being and for eudaimonic well-being for each set of genes were then averaged. (For the set of all 53 genes, the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 before averaging.)

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		**Eudaimonic**	
		Coefficient	***p***	**Coefficient**	***p***
Omnibus	53	0.01560	.5150	0.00743	.7568
Type I interferon viral response genes	31	0.00722	.7640	0.00319	.8946
Antibody synthesis genes	3	0.00842	.9076	0.06671	.3567
Pro-inflammatory genes	19	0.05664	.2236	0.03645	.4348

Table 4: Simple Regression Coefficients for Sets of Averaged Gene Expressions Predicted From Hedonic Well-Being or Eudaimonic Well-Being.

Note: The gene expressions were averaged across genes in each set of genes. Each of the eight regression analyses was based on 76 cases and predicted averaged gene expression from either hedonic well-being or eudaimonic well-being for one set of genes. Following Fredrickson et al. (2013), the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 for inclusion in the omnibus set of genes. The *p* values were not adjusted for multiple comparisons.

A two-tailed one-sample *t* test was then used to test each mean partial regression coefficient against zero. The standard error for each *t* test was not computed from the partial regression coefficients in each set; instead, the standard error was estimated by nonparametric bootstrapping (Efron & Tibshirani, 1993, pp. 45–59). These analyses produced the results reported by Fredrickson et al. (2013) that are shown in **Table 3**. The results of my three sets of reanalyses relating well-being to averaged (mean) gene association appear in **Tables 7, 8,** and **9**. The analyses for **Table 7**, like those for **Table 4**, used hedonic well-being alone or eudaimonic well-being alone as a predictor. The analyses for **Table 8**, like those for **Table 5**, used both hedonic well-being and eudaimonic well-being as predictors. The analyses for **Table 9**, like those for **Table 6**, used hedonic well-being, eudaimonic well-being, and the 15 covariates as predictors.

It is not clear why Fredrickson et al. (2013) did not test the difference between the mean partial regression coefficient for hedonic well-being and the mean partial regression coefficient for eudaimonic well-being for each set of genes as well as testing each mean partial regression coefficient against zero (as shown in **Table 3**), in analyses analogous to the tests of the difference between the correlations performed for the three depression variables and for total well-being. Given that (with one exception) the mean partial regression coefficients had different signs, perhaps they did not consider such a test necessary. Alternatively, this omission may have been an oversight; a more recent article by Fredrickson et al. (2015) did do such an analysis.

Brown et al. (2014) considered Fredrickson et al.'s (2013) analytic procedure to be "unnecessarily complicated" (p. 12708) and suggested the alternative of regressing the predictor variables on the averaged gene expression. Cole and Fredrickson (2014) countered that this alternative "guarantees bias" (p. E3581). This is not so. Although perhaps not intuitively obvious, the averaged (mean) regression coefficients for each set of genes equal the regression coefficients for the averaged (mean) gene expression for each set of genes, as can be seen by comparing the entries

in columns 3 and 5 in **Tables 7**, **8**, and **9** (averaged coefficients) to the corresponding entries in columns 3 and 5 in **Tables 4**, **5**, and **6** (averaged gene expressions). Note, though, that the *p* values associated with the regression coefficients in **Tables 7**, **8**, and **9** are usually lower than the corresponding *p* values in **Tables 4**, **5**, and **6**. Moreover, the *p* values for the regression coefficients in **Table 3** reported by Fredrickson et al. (2013) do not match those in either **Table 6** or **Table 9**, even though these three sets of regression coefficients were obtained from the prediction of gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates. The reasons for these differences will become apparent later when I examine the way that the *p* values were computed by Fredrickson et al. (2013).

Analysis of Suppression Effects

Why have the signs of some of the regression coefficients in the analyses predicting averaged gene expression (**Tables 5** and **6**) or averaged gene association (**Tables 8** and **9**) from both hedonic well-being and eudaimonic well-being reversed compared to those in the analyses predicting averaged gene expression (**Table 4**) or averaged gene association (**Table 7**), respectively, from hedonic well-being alone or eudaimonic well-being alone, and what implications do these reversals have for the differential relations of hedonic well-being and eudaimonic well-being to gene expression expected and reported by Fredrickson et al. (2013)?

Fredrickson and her co-authors insisted in their original article (2013) and in their reply (2013) to Coyne (2013) that the differential relations of hedonic well-being and eudaimonic well-being to gene expression were not due to the high correlation between hedonic well-being and eudaimonic well-being. Fredrickson and her co-authors were wrong.

Apparently anticipating criticism of their regression analyses that used highly correlated predictors, Fredrickson et al. (2013) substituted total well-being (eudaimonic well-being plus hedonic well-being) and relative eudaimonic predominance (eudaimonic well-being minus hedonic

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Coefficient	*p*	Coefficient	*p*
Omnibus	53	0.02689	.5039	–0.01410	.7258
Type I interferon viral response genes	31	0.01300	.7476	–0.00722	.8581
Antibody synthesis genes	3	–0.12523	.2999	0.16696	.1682
Pro-inflammatory genes	19	0.07644	.3270	–0.02474	.7504

Table 5: Partial Regression Coefficients for Sets of Averaged Gene Expressions Predicted From Hedonic Well-Being and Eudaimonic Well-Being.

Note: The gene expressions were averaged across genes in each set of genes. Each of the four regression analyses was based on 76 cases and predicted averaged gene expression from both hedonic well-being and eudaimonic well-being for one set of genes. Following Fredrickson et al. (2013), the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 for inclusion in the omnibus set of genes. The *p* values were not adjusted for multiple comparisons.

well-being) for hedonic well-being and eudaimonic well-being in "ancillary analyses" (p. 13685) to "ensure that differential gene expression estimates were not distorted by the high correlation of hedonic and eudaimonic well-being" (p. 13685). They reported that these two new variables were correlated only modestly ($r = .21$), and that there was no significant relation of total well-being to expression of the omnibus set of genes, but a significant negative relation of relative eudaimonic predominance to expression of the omnibus set of genes, stemming primarily from the significant negative relation of relative eudaimonic predominance to expression of the subset of pro-inflammatory genes.

The logic and the details of these ancillary analyses were not made clear in the original article. In their reply to Coyne (2013), Cole and Fredrickson (2013, p. E4814) expanded the description of these analyses:

Might the correlation between hedonic and eudaimonic well-being lead to erroneous conclusions? We addressed this possibility in a reparameterized analysis of gene expression reported in the Results .... If eudaimonic and hedonic scales were truly interchangeable, then only their shared variance (the sum, eudaimonic + hedonic) would systematically correlate with gene expression, and their unique/unshared variance (the difference, eudaimonic – hedonic) would reflect only random measurement error and would not correlate systematically with gene expression. Neither was the case. Gene expression associated only with the difference, and the sum and difference variables were not highly correlated .... Even in the presence of correlated predictor variables and control for confounders, the general linear model parameter estimates we used are well established ... to remain unbiased, and their *P* values remain accurate. [Correlated predictors and multiple covariates increase the sampling variability of point estimates, but their SEs adjust appropriately

.... Correlated predictors might potentially lead to conservative false-negative errors in statistical testing, but they would not induce false-positive errors.] Thus, there is no reason for concern that the standard multivariate analyses we used led to inaccurate conclusions.

This expanded description is confusing rather than enlightening and contains several inaccurate statements:

· The shared variance between two variables is not their sum; it is the square of their correlation (r^2).
· The unique/unshared variance between two variables is not their difference; it is one minus the square of their correlation ($1 – r^2$).
· It is not true that a predictor that has a correlation with the criterion reflecting only measurement error (near zero, presumably) cannot correlate with that criterion in a regression containing two (or more) predictors; a correlation of zero (or nearly zero) can become nonzero and increase the magnitude of the other predictor. This well-known regression situation is called "traditional suppression."
· It is not true that correlated predictors cannot induce false-positive errors. If two predictors are correlated, measurement error in one of them can inflate the false-positive (Type I) error in tests of the other (Brunner & Austin, 2009; Shear & Zumbo, 2013). This is a moot point in Fredrickson et al.'s (2013) study, however, because, of the 106 possible tests of the coefficients for hedonic well-being and eudaimonic well-being (53 tests each) in the regression analyses that predicted gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates, only one was significant.
· Traditionally, the "standard multivariate analys[i]s" (p. E4184) for predicting multiple criteria from the same predictors for the same cases is multivariate multiple regression; it is not a set of multiple regression analyses predicting one criterion at a time, like

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Coefficient	*p*	Coefficient	*p*
Omnibus	53	0.01276	.7667	−0.02717	.5378
Type I interferon viral response genes	31	0.01661	.6803	0.03074	.4574
Antibody synthesis genes	3	−0.03899	.7290	0.09016	.4350
Pro-inflammatory genes	19	0.05654	.4729	−0.01140	.8874

Table 6: Partial Regression Coefficients for Sets of Averaged Gene Expressions Predicted From Hedonic Well-Being, Eudaimonic Well-Being, and 15 Covariates.
Note: The gene expressions were averaged across genes in each set of genes. Each of the four regressions was based on 76 cases and predicted averaged gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates. Following Fredrickson et al. (2013), the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 for inclusion in the omnibus set of genes. The *p* values were not adjusted for multiple comparisons.

that of Fredrickson et al. (2013). A modern alternative to multivariate multiple regression is mixed-effects linear modeling with the gene expressions treated as repeated measurements, which Brown et al. (2014, Supporting Information, p. 16) suggested. Both of these analytic methods take into account the dependency in the analyses; a set of multiple regression analyses predicting one criterion at a time does not. More-over, even though each of Fredrickson et al.'s (2013) individual regression analyses might be considered standard in and of itself, their method of computing p values for those analyses cannot, as will be seen.

In their Figure 1B, Fredrickson et al. (2013, p. 13686) provided without explanation what they called a "Tukey mean-difference plot," although it is actually a "Tukey sum-difference plot," usually called a "Bland-Altman plot" (Altman & Bland, 1983) in the medical literature. This plot shows the relation between total well-being and relative eudaimonic predominance. Plots like this are often used to determine whether two measures, tests, or instruments can be used interchangeably; the common belief (e.g., Coyne, 2013) that a high correlation between two measures indicates that those measures are interchangeable is not correct. Usually horizontal lines are drawn across a Bland-Altman plot at the mean of the measure on the y axis, and at 1.96 (or 2) standard deviations above and below that mean. The two measures are judged interchangeable if all the graphed sum-difference data points fall between the lines at 1.96 standard deviations above and below the mean, called the "lines of agreement." Fredrickson et al.'s (2013) plot of the relation between total well-being and relative eudaimonic prevalence is ambiguous with respect to whether hedonic well-being and eudaimonic well-being are interchangeable. A few data points fall outside the lines of agreement (which were not drawn), but only a few. But even if one concludes that hedonic well-being and eudaimonic well-being are not interchangeable, one

cannot then conclude that the high correlation between these two predictors cannot be responsible for their differential relations to the criterion, as Fredrickson and her co-authors would have it. And, as will become evident shortly, Fredrickson et al.'s (2013) regression analyses did not in fact create "purified" indices of hedonic well-being and eudaimonic well-being, as claimed.

A comparison of simple regression coefficients to partial regression coefficients demonstrates that the high correlation between hedonic well-being and eudaimonic well-being was in fact partly responsible for the differential relations of these two well-being variables to gene expression in Fredrickson et al.'s (2013) study. Researchers often seem to believe that in a regression analysis predicting a criterion variable Y from two predictor variables X_1 and X_2, one or the other of two situations must occur: either X_1 and X_2 are *independent*, or X_1 and X_2 are *redundant*:

· *Independence* occurs when the two predictors are un-correlated. The partial regression coefficient for each of the two predictors equals its corresponding simple regression coefficient. (For simplicity and generality, I will assume that the predictors and the criterion are standardized. The simple regression coefficient for X_1 or X_2 is obtained by regressing Y on either X_1 alone or X_2 alone, respectively. The simple regression coefficient is equivalent to the zero-order correlation between the predictor and the criterion. The partial regression coefficient for X_1 and for X_2 is obtained by regressing Y on both X_1 and X_2. Partial regression coefficients are not correlations. In the Fredrickson et al., 2013, study, the predictors hedonic well-being and eudaimonic well-being were standardized, but the criterion gene expression was not. The relations to be described still apply, but the simple regression coefficient is not equivalent to the correlation.)
· *Redundancy* occurs when the two predictors are correlated. The magnitude (absolute value) of each partial

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Coefficient	p	Coefficient	p
Omnibus	53	0.01560	.1318	0.00743	.4694
Type I interferon viral response genes	31	0.00722	.5294	0.00319	.8018
Antibody synthesis genes	3	0.00842	.5881	0.06671	.2011
Pro-inflammatory genes	19	0.05664	.0065	0.03645	.0427

Table 7: Averaged Simple Regression Coefficients for Sets of Gene Expressions Predicted From Hedonic Well-Being or Eudaimonic Well-Being.

Note: The gene expression of each gene was predicted from either hedonic well-being or eudaimonic well-being. Each of the 106 regression analyses (53 for hedonic well-being and 53 for eudaimonic well-being) was based on 76 cases. The simple regression coefficients for each set of genes were then averaged across the genes in the set. Following Fredrickson et al. (2013), the simple regression coefficients for the Type I interferon viral response genes and the antibody synthesis genes were weighted by –1 for inclusion in the omnibus set of genes. The p values were not adjusted for multiple comparisons.

regression coefficient is less than the magnitude of its corresponding simple regression coefficient, but the sign is unchanged. This is the situation to which Fredrickson et al. (2013) were referring when they claimed that their regression analyses used "purified" indices of hedonic well-being and eudaimonic well-being.

In fact, three other situations are possible when the two predictors are correlated: *cooperative suppression, traditional suppression,* and *negative suppression* (Tzelgov & Henik, 1991).

- *Cooperative suppression* (also called *reciprocal suppression*) occurs when the correlation between one predictor and the criterion is positive, the correlation between the other predictor and the criterion is negative, and the correlation between the two predictors is positive (or the scale of one of the variables can be reversed so that the correlations exhibit this pattern). The magnitude of the partial regression coefficient for each of the two predictors is greater than the magnitude of its corresponding simple regression coefficient, but the sign is unchanged.
- *Traditional suppression* (also called *classical suppression*) occurs when the two predictors are correlated, and the correlation of one of the predictors with the criterion equals zero (or sometimes, nearly zero). The partial regression coefficient for the predictor having the zero correlation with the criterion is non-zero. The magnitude of the partial regression coefficient for the predictor having the non-zero correlation with the criterion is greater than the magnitude of its corresponding simple regression coefficient; the sign is unchanged.
- *Negative suppression* (also called *net suppression*) occurs when the two predictors are correlated, and the partial regression coefficient for one of the predictors has a sign that is reversed from that of its corresponding simple regression coefficient. The partial regression coefficient with the sign

that reversed is for the predictor for which the magnitude of the simple regression coefficient is smaller. Negative suppression can occur in one of two ways: (a) the magnitude of the simple regression coefficient for X_1 is greater than that for X_2, and the magnitude of the correlation between the two predictors is greater than the ratio of the magnitude of the simple regression coefficient for X_2 to the magnitude of the simple regression coefficient for X_1; or (b) the magnitude of the simple regression coefficient for X_2 is greater than that for X_1, and the magnitude of the correlation between the two predictors is greater than the ratio of the magnitude of the simple regression coefficient for X_1 to the magnitude of the simple regression coefficient for X_2. The magnitude of the partial regression coefficient with the sign that reversed can be less than, equal to, or greater than the magnitude of its corresponding simple regression coefficient. The magnitude of the partial regression coefficient with the sign that did not reverse is greater than the magnitude of its corresponding simple regression coefficient.

Thus, suppression can cause sign reversals in, and increase the magnitudes of, regression coefficients. The occurrence of traditional suppression or cooperative suppression does not depend on the magnitude of the correlation between the two predictors, but negative suppression is more likely to occur when the correlation between the two predictors is high, as it was in Fredrickson et al.'s (2013) study. The majority of the 53 regression analyses predicting gene expression from hedonic well-being and eudaimonic well-being were characterized by negative suppression. This suppression resulted in the apparent differential relations of hedonic well-being and eudaimonic well-being to gene expression.

The regression-analysis results for the subset of three antibody synthesis genes shown in the middle section of **Table 10** provide a small example. For simplicity and clarity, I will compare the results of the regression analyses using hedonic well-being alone (column 2) or eudaimonic well-being alone (column 3) as predictors

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Coefficient	*p*	Coefficient	*p*
Omnibus	53	0.02689	.0150	−0.01410	.1928
Type I interferon viral response genes	31	0.01300	.0882	−0.00722	.5417
Antibody synthesis genes	3	−0.12523	.2072	0.16696	.1967
Pro-inflammatory genes	19	0.07644	.0005	−0.02474	.0667

Table 8: Averaged Partial Regression Coefficients for Sets of Gene Expressions Predicted From Hedonic Well-Being and Eudaimonic Well-Being.

Note: The gene expression of each gene was predicted from both hedonic well-being and eudaimonic well-being. Each of the 53 regression analyses was based on 76 cases. The partial regression coefficients for each set of genes were then averaged across the genes in the set. Following Fredrickson et al. (2013), the partial regression coefficients for the Type I interferon viral response genes and the antibody synthesis genes were weighted by −1 for inclusion in the omnibus set of genes. The *p* values were not adjusted for multiple comparisons.

to those including both well-being variables (columns 4 and 5) as predictors, omitting the 15 covariates. The simple regression coefficients for gene expression predicted from hedonic well-being alone and from eudaimonic well-being alone are small and with one exception, positive (hedonic well-being: 0.02882, –0.01621, and 0.01265 for genes IGJ, IGLL1, and IGLL3, respectively; eudaimonic well-being: 0.13347, 0.05429, and 0.01236 for genes IGJ, IGLL1, and IGLL3, respectively). The averaged associations (simple regression coefficients) are therefore 0.00842 and 0.06671 for hedonic well-being and eudaimonic well-being, respectively, and do not show the differential relations to gene expression expected and reported by Fredrickson et al. (2013).

Compare these simple regression coefficients to the partial regression coefficients obtained when gene expression is predicted from both hedonic well-being and eudaimonic well-being. The regression analysis for gene IGLL3 shows redundancy; the partial regression coefficients for hedonic well-being (0.00767) and eudaimonic well-being (0.00623) have the same signs (positive) as, and are smaller in magnitude than, their corresponding simple regression coefficients (0.01265 and 0.01236, respectively). The other two regression analyses show suppression effects. The regression analysis for gene IGLL1 shows cooperative suppression; the relation between hedonic well-being and gene expression has a different sign (negative) than the relation between eudaimonic well-being and gene expression and the relation between hedonic well-being and eudaimonic well-being (both positive). The partial regression coefficients for both hedonic well-being and eudaimonic well-being (–0.16613 and 0.18728, respectively) have the same signs as, but are much larger in magnitude than, their corresponding simple regression coefficients (–0.01621 and 0.05429, respectively). The regression analysis for gene IGJ shows negative suppression. The partial regression coefficient for hedonic well-being (–0.21724) has a sign reversed from that of its corresponding simple regression coefficient (0.02882) and is much larger in magnitude. The partial regression coefficient for eudaimonic well-being (0.30737) has the same sign as

its corresponding simple regression coefficient (0.13347) but is much larger in magnitude. Now the averaged associations (partial regression coefficients) are –0.12523 and 0.16696 for hedonic well-being and eudaimonic well-being, respectively. Although these averaged coefficients are not significant, their different signs are consistent with the expected differential relations of hedonic well-being and eudaimonic well-being to gene expression. The sign of the relation between hedonic well-being and gene expression is now negative, whereas the sign of the relation between eudaimonic well-being and gene expression is positive, just as Fredrickson et al. (2013) expected and reported.

The coefficients from all 53 regression analyses predicting gene expression from (a) hedonic well-being alone, (b) eudaimonic well-being alone, and (c) both hedonic well-being and eudaimonic well-being are shown in **Table 10**. Thirty-three of the 53 sets of regression analyses show suppression effects (mostly negative suppression). These effects are responsible for the reversals in regression-coefficient signs and increases in regression-coefficient magnitudes that led Fredrickson et al. (2013) to conclude that hedonic well-being and eudaimonic well-being have differential relations to gene expression. In turn, the negative suppression results from the high correlation between hedonic well-being and eudaimonic well-being (.79 as reported by Fredrickson et al., 2013; .80 in the corrected sample of 76 usable cases). If the correlation had been low, few of the 53 sets of regression analyses would have shown suppression, and differential relations of hedonic well-being and eudaimonic well-being to gene expression would not have been evident.

Interestingly, Brown et al. (2014), in their analysis of the relation of each of the 8,191 possible two-factor scorings of the MHC–SF to gene expression, briefly mentioned "a previously reported phenomenon (1), whereby when two highly-correlated items are incorporated in a regression analysis, their variance is distributed approximately equally, but with appreciate opposite signs, across the two resulting regression coefficients" (Supporting Information, p. 27). Reference 1 is a review of data-reduction techniques

Gene Set	Number of Genes	Relation to Well-Being			
		Hedonic		Eudaimonic	
		Coefficient	*p*	Coefficient	*p*
Omnibus	53	0.01276	.0969	−0.02717	.0033
Type I interferon viral response genes	31	0.01661	.0171	0.03074	.0109
Antibody synthesis genes	3	−0.03898	.2618	0.09016	.1579
Pro-inflammatory genes	19	0.05654	.0001	−0.01140	.0667

Table 9: Averaged Partial Regression Coefficients for Sets of Gene Expressions Predicted From Hedonic Well-Being, Eudaimonic Well-Being, and 15 Covariates.

Note: The gene expression of each gene was predicted from hedonic well-being, eudaimonic well-being, and the 15 covariates. Each of the 53 regression analyses was based on 76 cases. The partial regression coefficients for each set of genes were then averaged across the genes in the set. Following Fredrickson et al. (2013), the partial regression coefficients for the Type I interferon viral response genes and the antibody synthesis genes were weighted by −1 for inclusion in the omnibus set of genes. The *p* values were not adjusted for multiple comparisons.

in electroencephalographic research (Allen, Coan, & Nazarian, 2004). The reported phenomenon appears to be a special case of negative suppression, although it is not called such.

Moreover, the inclusion of the 15 covariates in the regression analysis for each gene creates additional suppression effects; this is the reason for the regression coefficient for eudaimonic well-being for the subset of Type I interferon viral response genes having a negative sign in **Tables 5** and **8** reversing to a positive sign in **Tables 6** and **9**, after having reversed from a positive sign in **Tables 4** and **7** to a negative sign in **Tables 5** and **8**.

What is one to make of all these sign reversals? Are the signs of the final regression coefficients (those in **Tables 6** and **9**) "real," indicating the direction of the true biological relation between each of the two well-being variables and gene expression, or are they merely statistical artifacts, lacking the theoretical importance bestowed on them by Fredrickson et al. (2013)?

Unfortunately, it is difficult to know without more information than is included in the dataset, but a comparison of the results of regression analyses predicting averaged gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates to the results of analogous regression analyses that replace eudaimonic well-being with Keyes's (2009a) social well-being and psychological well-being is suggestive. **Table 11** presents the partial regression coefficients that would have been obtained had Fredrickson et al. (2013) used the documented and well-validated three-factor scoring instead of their idiosyncratic two-factor scoring and corrected the afore-mentioned miscoding of race/ethnicity. (None of these three well-being variables, which are highly correlated with one another, has a significant relation with averaged gene expression when used as the sole predictor.) A comparison of the partial regression coefficients in **Table 11** to those in **Tables 6** and **9** shows that the relation of emotional (hedonic) well-being to averaged gene expression has reversed sign for the omnibus set of genes, which should not have happened. Moreover, the sign of the relation of social well-being to averaged gene expression is the same as the sign of the relation of eudaimonic well-being to averaged gene expression for each of the four sets of genes, but the sign of the relation of psychological well-being to averaged gene expression is the reverse of the sign of the relation of eudaimonic well-being to averaged gene expression for each of the four sets of genes. That is, the signs of the four coefficients for psychological well-being are reversals of the signs of the four coefficients for social well-being. If social well-being and psychological well-being can legitimately be represented by the single construct of eudaimonic well-being, as Cole and Fredrickson (2014, article, p. E3581, Supporting Information, pp. 16, 22, 27) insisted in their reply to Brown et al. (2014), then surely their relations to averaged gene expression should have the same direction. But they do not, suggesting that the direction and magnitude of the partial regression coefficients in Fredrickson et al.'s (2013) study are statistical artifacts.

Although traditionally suppression effects have been viewed as statistical curiosities, artifacts, or nuisances (Bobko, 2001), they may be of theoretical interest, as, for example, in the relation of guilt and shame to self-reported aggression (Paulhus, Robins, Trzesniewski, & Tracy, 2004; see also Nickerson, 2008). Determination of whether a suppression effect is a statistical artifact or a phenomenon of substantive interest requires strong theoretical reasoning. No such reasoning appeared in Fredrickson et al. (2013); indeed, the existence of the suppression effects was not even recognized. Of course, little or no attention is usually paid to regression coefficients that are not significant, regardless of which of the five situations described above applies to a particular regression analysis.

Computation of P Values

The question of significance for the regression coefficients brings us to the computation of p values. As I noted earlier, the p values for the regression coefficients in **Table 9** are different from those reported by Fredrickson et al. (2013), shown in **Table 3**, and the p values associated with the regression coefficients in **Tables 7**, **8**, and **9** are usually lower than the p values associated with the regression coefficients in **Tables 4**, **5**, and **6**. Indeed, some of the regression coefficients reported in **Tables 7**, **8**, and **9** are significant, when their corresponding and equal regression coefficients reported in **Tables 4**, **5**, and **6** are not.

One reason why the p values in **Table 9** are different from those reported by Fredrickson et al. (2013) is the uncorrected value ("4") for race/ethnicity for one case in Fredrickson et al.'s (2013) dataset. As noted by Brown et al. (2014, Supporting Information, p. 24), this seemingly small error had a surprisingly large effect on the results (especially those for hedonic well-being) obtained by Fredrickson et al. (2013). For example, had this error not been corrected, the averaged partial regression coefficient for hedonic well-being for the omnibus set of genes shown in **Table 9** would equal 0.02801 instead of the correct 0.01276; for the subset of antibody synthesis genes that coefficient would equal –0.07938 instead of the correct –0.03898.

A second reason is that Fredrickson et al. (2013) did not use the standard error computed across the regression coefficients for each set of genes in computing the one-sample t test for that set of genes, as I have done. Instead, they bootstrapped the standard error "to estimate a stable SE, as recommended" (Supporting Information, p. 2). Bootstrapping is useful when the theoretical distribution of a statistic is mathematically complicated or unknown; if an assumption, such as the normality assumption, of a statistical test is violated (as it is in Fredrickson et al.'s, 2013, one-sample t tests); if the number of observations is too small for valid inference from a statistical test (also the case in some of Fredrickson et al.'s, 2013, one-sample t tests); and so on. Each run of a bootstrapping algorithm would yield a different standard error, so it is unlikely that a p value for a t value based on a computed standard error would exactly equal one based on a bootstrapped standard error.

| Gene | Well-Being Coefficients from Regression Analyses | | | | | | |
| | Simple | | Partial | | Suppression | | |
	Hedonic	Eudaimonic	Hedonic	Eudaimonic	Type[a]	Keeps Sign, Larger[b,c]	Reverses Sign, Change[b,d]
Type I interferon viral response genes							
IFIT1L	−0.22554	−0.28774	0.01339	−0.29847	N	E	H, <
GBP1	−0.00648	−0.01402	0.01319	−0.02457	N/T	E	H, >
IFI16	−0.05918	−0.04820	−0.05735	−0.00228	R		
IFI27	−0.04127	−0.04985	−0.00381	−0.04680	R		
IFI27L1	0.00090	0.00608	−0.01107	0.01494	N/T	E	H, >
IFI27L2	−0.00669	−0.02652	0.04049	−0.05893	N/T	E	H, >
IFI30	−0.04097	−0.06427	0.02918	−0.08763	N	E	H, <
IFI35	−0.01653	−0.01819	−0.00549	−0.01379	R		
IFI44	0.05094	0.03443	0.06509	−0.01768	N	H	E, <
IFI44L	0.06188	0.03970	0.08381	−0.02740	N	H	E, <
IFI6	0.02280	0.00773	0.04625	−0.02930	N/T	H	E, >
IFIH1	−0.02290	−0.01186	−0.03731	0.01801	N	H	E, >
IFIT1	0.11698	0.10981	0.08096	0.04500	R		
IFIT2	0.12863	0.10301	0.12853	0.00012	R		
IFIT3	0.09687	0.09764	0.05211	0.05592	R		
IFIT5	−0.00534	−0.01015	0.00775	−0.01636	N/T	E	H, >
IFITM1	0.05282	0.06572	0.00058	0.06525	R		
IFITM2	0.04722	0.05074	0.01838	0.03603	R		
IFITM3	0.00154	0.02236	−0.04554	0.05882	N/T	E	H, >
IFITM4P	0.00604	0.00236	0.01154	−0.00687	N/T	H	E, >
IFITM5	−0.00258	0.00031	−0.00788	0.00662	C		
IFNB1	0.00176	0.00527	−0.00683	0.01073	N/T	E	H, >
IRF2	−0.01620	−0.00357	−0.03714	0.02616	N/T	H	E, >
IRF7	0.03038	0.02622	0.02617	0.00527	R		
IRF8	−0.04512	−0.04886	−0.01671	−0.03548	R		
MX1	0.04966	0.06555	−0.00784	0.07183	N	E	H, <
MX2	0.00680	0.00833	0.00037	0.00803	R		
OAS1	−0.03414	−0.02493	−0.03948	0.00668	N	H	E, <
OAS2	−0.01613	−0.01888	−0.00283	−0.01662	R		
OAS3	0.03921	0.03001	0.04226	−0.00382	N	H	E, <
OASL	0.04847	0.05055	0.02228	0.03271	R		
Antibody synthesis genes							
IGJ	0.02882	0.13347	−0.21724	0.30737	N	E	H, >
IGLL1	−0.01621	0.05429	−0.16613	0.18728	C		
IGLL3	0.01265	0.01236	0.00767	0.00623	R		
Pro-inflammatory genes							
IL1B	0.14056	0.07545	0.22321	−0.10324	N	H	E, >
IL8	0.31637	0.27763	0.26206	0.06784	R		

Well-Being Coefficients from Regression Analyses

Gene	Simple		Partial		Suppression		
	Hedonic	Eudaimonic	Hedonic	Eudaimonic	Type[a]	Keeps Sign, Larger[b,c]	Reverses Sign, Change[b,d]
FOS	0.08753	0.08685	0.05013	0.04672	R		
FOSB	0.10143	0.03996	0.19333	−0.11481	N	H	E, >
FOSL1	0.00906	−0.01412	0.05669	−0.05950	C		
FOSL2	0.04684	0.02441	0.07603	−0.03645	N	H	E, >
IL1A	0.02405	0.00562	0.05444	−0.03796	N/T	H	E, >
IL6	0.02493	0.00607	0.05588	−0.03866	N/T	H	E, >
JUN	0.05045	0.05132	0.02609	0.03043	R		
JUNB	0.01093	0.01348	0.00038	0.01318	R		
JUND	0.01012	0.01129	0.00300	0.00890	R		
NFKB1	0.00495	0.01334	−0.01596	0.02612	N/T	E	H, >
NFKB2	0.01921	0.01213	0.02645	−0.00904	N	H	E, <
PTGS1	−0.07327	−0.10879	0.03849	−0.13961	N	E	H, <
PTGS2	0.13299	0.09750	0.15297	−0.02496	N	H	E, <
REL	0.02267	0.00957	0.04180	−0.02389	N/T	H	E, >
RELA	0.03548	0.03662	0.01716	0.02288	R		
RELB	0.03214	0.01189	0.06300	−0.03855	N	H	E, >
TNF	0.07968	0.04242	0.12730	−0.05948	N	H	E, >

Table 10: Suppression Effects.

Note: The simple regression coefficients were obtained from regression analyses that predicted gene expression from either hedonic well-being or eudaimonic well-being. The partial regression coefficients were obtained from regression analyses that predicted gene expression from both hedonic well-being and eudaimonic well-being.

[a] R = redundancy, C = cooperative suppression, N = negative suppression, T = traditional suppression, N/T = negative or traditional suppression. It can be difficult to distinguish between negative suppression and traditional suppression when one or both of the simple regression coefficients are very small. Here the somewhat arbitrary strategy of coding as N/T when the magnitude of one or both of the simple regression coefficients is less than .01 has been adopted.

[b] H = hedonic well-being, E = eudaimonic well-being.

[c] For negative or traditional suppression, H or E indicates the well-being variable for which the sign of the partial regression coefficient is the same as the sign of the corresponding simple regression coefficient. The magnitude of the partial regression coefficient is greater than the magnitude of the corresponding simple regression coefficient.

[d] For negative or traditional suppression, H or E indicates the well-being variable for which the sign of the partial regression coefficient is the reverse of the sign of the corresponding simple regression coefficient. The magnitude of the partial regression coefficient may be less than (<), equal to (=), or greater than (>) the magnitude of the corresponding simple regression coefficient.

As noted earlier, some of the regression coefficients reported in **Tables 7**, **8**, and **9** are significant, when their corresponding and equal regression coefficients reported in **Tables 4**, **5**, and **6** are not. For example, in **Table 6**, the coefficient for eudaimonic well-being in the regression analysis predicting gene expression averaged across all 53 genes from hedonic well-being, eudaimonic well-being, and the 15 covariates for 76 cases equals −0.02717. The standard error for this coefficient equals 0.04383, $t = −0.62$, $p = .5378$, $n = 76$, not significant. In **Table 9**, the average of the partial regression coefficients for eudaimonic well-being from the 53 regression analyses predicting gene expression from hedonic well-being, eudaimonic well-being, and the 15 covariates also equals −0.02717. But the standard error for this averaged coefficient equals 0.00882, $t = −3.08$, $p = .0033$, $n = 53$, significant.

The reason why some of the regression coefficients reported in **Tables 7**, **8**, and **9** are significant, when their corresponding and equal regression coefficients reported in **Tables 4**, **5**, and **6** are not, is that the standard errors for the statistical tests reported in **Tables 7**, **8**, and **9** are computed differently from the standard errors for the statistical tests reported in **Tables 4**, **5**, and **6**.

Gene Set	Number of Genes	Coefficients for Relation to Well-Being		
		Emotional	**Social**	**Psychological**
Omnibus	53	−0.00907	−0.06839	0.05665
Type I interferon viral response genes	31	0.04392	0.08317	−0.07207
Antibody synthesis genes	3	−0.00078	0.14135	−0.07546
Pro-inflammatory genes	19	0.04623	−0.03275	0.02851

Table 11: Partial Regression Coefficients for Sets of Averaged Gene Expressions Predicted From Emotional Well-Being, Social Well-Being, Psychological Well-Being, and 15 Covariates.

Note: The gene expressions were averaged across genes in each set of genes. Each of the four regressions was based on 76 cases and predicted averaged gene expression from emotional well-being, social well-being, psychological well-being, and the 15 covariates. Following Fredrickson et al. (2013), the Type I interferon viral response genes and the antibody synthesis genes were weighted by −1 for inclusion in the omnibus set of genes.

For the latter tests, the standard errors are based on the variation in the criterion variable and the predictor variables, and the covariation between these variables, across the 76 cases for each set of genes. For the former tests, the standard errors are based on the variation in regression coefficients across the genes (n = 53, 31, 3, or 19) for each set of genes. (These are very small sample sizes for statistical tests, especially n = 3.) Which sets of p values are correct, those in **Tables 4**, **5**, and **6**, or those in **Tables 7**, **8**, and **9**?

The p values in **Tables 4**, **5**, and **6**—not those in **Tables 7**, **8**, and **9**—are correct, for (at least) two reasons. First, Fredrickson et al.'s (2013) method of computing p values treats two regression coefficients of the same value as equivalent. But one of those regression coefficients may have a large standard error and a wide confidence interval, whereas the other may have a small standard error and a narrow confidence interval. Moreover, one regression coefficient may have a confidence interval that includes zero and so is not significant, whereas the other may have a confidence interval that does not include zero and so is significant. That is, Fredrickson et al.'s (2013) method of computing p values discarded valuable information about the accuracy of the regression coefficients and left ambiguous the direction of the relation between the criterion and the predictor (Kelley & Maxwell, 2003). Unfortunately, the partial regression coefficients for hedonic well-being and eudaimonic well-being in Fredrickson et al.'s (2013) study all have wide confidence intervals, probably as a result of the effects of the well-being variables on gene expression being small, the well-being variables being highly correlated, and the use of a sample size of 76 that is much too small for the large number (17) of predictors. Thus, the partial regression coefficients for hedonic well-being and eudaimonic well-being are unlikely to be accurate. Moreover, all but one of the 106 partial regression coefficients have confidence intervals that include zero, so that the directions of the relations between the criterion and the predictors of interest are not certain. This is so for both the partial regression coefficients from the analyses predicting individual gene expression and for the partial regression coefficients from the analyses predicting averaged gene expression.

Second, the observations in Fredrickson et al.'s (2013) one-sample t tests—the partial regression coefficients—were not independent, which invalidates these tests. The one-sample t test assumes that observations are randomly and independently drawn from a normally distributed population. The observations in Fredrickson et al.'s (2013) t tests did not satisfy this requirement. These observations were the 106 partial regression coefficients that had been sorted into eight sets. These coefficients were not independent because they were computed from 53 regression analyses that used the same cases and the same predictor variables; only the criterion variable (expression for a particular gene) varied. Moreover, the sets of genes were specifically selected a priori on the basis of their similarity in biological functioning, so they were not independent, either.

The one-sample t test is robust to moderate violations of the normality assumption, but it is not robust to violations of the independence assumption. The nonindependence of observations both increases the probability of false-positive (Type I) errors and decreases the probability of false-negative (Type II) errors. As the number of observations that are pairwise-correlated increases and as the magnitude of the correlation between the observations increases, the probability of a false-positive error increases rapidly. For example, for 40 observations having a (population) intercorrelation of .30, an apparent p value of .05 is actually about .347 (Zimmerman, Williams, & Zumbo, 1992, **Table 2**, p. 1017).

Brown et al. (2014, Supporting Information, p. 16) remarked that they had been unable to locate any other studies using the analytic method of Fredrickson et al. (2013). Cole and Fredrickson (2014) replied that "pooling gene associations [for use in a one-sample t test] is actually commonplace and represents an elementary statistical sum of random variables" (p. 3581), but did not provide any examples of such pooling. Cole and Fredrickson (2014) have failed to distinguish between a sum of independent random variables and a sum of correlated (dependent) random variables. For independent random variables, the

mean is the sum of the means, and the variance is the sum of the variances. For correlated random variables, the mean is also the sum of the means, but it does not generally converge to the population mean, as the Law of Large Numbers states for independent random variables. Also, for correlated random variables, the variance is not the sum of the variances but takes the correlation into account. The variance for correlated random variables is smaller than the variance for independent random variables. Assuming that correlated random variables have the same variance as independent random variables, as Fredrickson et al. (2013) seem to have done, introduces bias in any computation using the variance (or its square root, the standard deviation).

Two recent studies (Knight et al., 2016; Vedhara et al., 2015) co-authored by one of the co-authors of the Fredrickson et al. (2013) study (Steven W. Cole) used the same analytic method as Fredrickson et al. (2013) but altered the bootstrapping method for generating standard errors for the one-sample t tests "to account for potential correlation among residuals across genes" (Knight et al., 2016, p. 71). This change to the analysis is a tacit admission that the computation of p values in Fredrickson et al.'s (2013) study was not correct, but no corrigendum to, or retraction of, that article has appeared.

Conclusions

As I have demonstrated, the statistical problems in Fredrickson et al.'s (2013) study cast considerable doubt on the validity of their conclusions that hedonic well-being and eudaimonic well-being have "similar affective correlates" but "markedly divergent gene transcriptional correlates in human immune cells". Generally, I agree with Coyne (2013) and with Brown et al. (2014) that Fredrickson et al.'s (2013) study is seriously flawed, although some of the specific points made by Coyne (2013) and Brown et al. (2014) were not quite on the mark. For example, Coyne (2013) was correct in asserting that the high correlation between hedonic well-being and eudaimonic well-being in Fredrickson et al.'s (2013) study was problematical, but not correct in stating that hedonic well-being and eudaimonic well-being were correlated to the degree that their respective internal consistencies allowed. (The maximum correlation between two variables equals the square root of the product of their reliabilities. Assuming that Cronbach's alpha is being used as the measure of reliability, the maximum correlation equals the square root of the product of .93 [for hedonic well-being] and .92 [for eudaimonic well-being], which equals .92, not .79.) Brown et al. (2014) were correct in asserting that the MHC–SF has a validated three-factor structure and scoring. But in analyzing the relation of each of the 8,191 possible two-factor scorings of the MHC–SF to gene expression, they, like Fredrickson et al. (2013), did not realize that their one-sample t tests violated the assumption of independence. Nonetheless, the letter to the editor of Coyne (2013), the reanalysis of Brown et al. (2014), and my review of the statistical problems in Fredrickson et al. (2013)'s analyses taken together strongly suggest that there is no good evidence for Fredrickson et al.'s (2013) claim that hedonic well-being and eudaimonic well-being are differentially related to gene expression or for their recommendation that, as regards disease prevention, hedonia is not the way to live (p. 13688).

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